

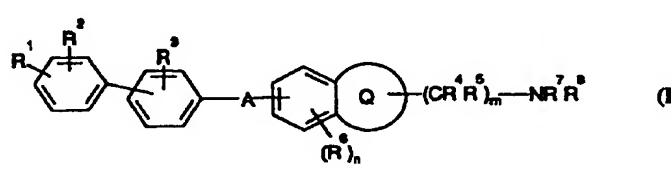
D2

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 413/12, A61K 31/55, 31/535, 31/40, 31/35		A1	(11) International Publication Number: WO 95/32967
		(43) International Publication Date: 7 December 1995 (07.12.95)	
(21) International Application Number: PCT/EP95/01890		(74) Agent: SUMMERSELL, Richard, John; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).	
(22) International Filing Date: 16 May 1995 (16.05.95)			
(30) Priority Data: 9410780.2 28 May 1994 (28.05.94) GB 9410781.0 28 May 1994 (28.05.94) GB		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).	
(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC (GB/GB); New Horizons Court, Brentford, Middlesex TW8 9EP (GB).			
(72) Inventors; and (75) Inventors/Applicants (for US only): HAM, Peter (GB/GB); SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). GASTER, Laramie, Mary (GB/GB); SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). KING, Francis, David (GB/GB); SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). DUCKWORTH, David, Malcolm (GB/GB); SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(54) Title: AMIDE DERIVATIVES HAVING 5HT _{1D} -ANTAGONIST ACTIVITY			
			
(57) Abstract			
<p>Compound of formula (I), processes for their preparation and their use as CNS agents are disclosed, in which A is CONR where R is hydrogen or C₁-alkyl; Q is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur; R¹ is hydrogen, halogen, C₁-alkyl, C₃-cycloalkyl, COC₁-alkyl, C₁-alkoxy, hydroxy, hydroxyC₁-alkyl, hydroxyC₁-alkoxy, C₁-alkoxyC₁-alkoxy, acyl, nitro, trifluoromethyl, cyano, SR⁹, SOR⁹, SO₂R⁹, SO₂NR¹⁰R¹¹, CO₂R¹⁰, CONR¹⁰R¹¹, CO₂NR¹⁰R¹¹, CONR¹⁰(CH₂)_aCO₂R¹¹, (CH₂)_aNR¹⁰R¹¹, (CH₂)_aCONR¹⁰R¹¹, (CH₂)_aNR¹⁰COR¹¹, (CH₂)_aCO₂C₁-alkyl, CO₂(CH₂)_aOR¹⁰, NR¹⁰R¹¹, NR¹⁰CO₂R¹¹, NR¹⁰CONR¹⁰R¹¹, CR¹⁰-NOR¹¹, CNR¹⁰-NOR¹¹, where R¹⁰ and R¹¹ are independently hydrogen or C₁-alkyl and a is 1 to 4 or R¹ is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur; R² and R³ are independently hydrogen, halogen, C₁-alkyl, C₃-cycloalkyl, C₃-cycloalkenyl, C₁-alkoxy, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO₂R¹⁰, CONR¹⁰R¹¹, NR¹⁰R¹¹ where R¹⁰ and R¹¹ are as defined for R¹; R⁴ and R⁵ are independently hydrogen or C₁-alkyl; R⁶ is halogen, hydroxy, C₁-alkyl or C₁-alkoxy; R⁷ and R⁸ are independently hydrogen, C₁-alkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5 to 7-membered heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen or sulphur; m is 0 to 4; and n is 0, 1 or 2.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

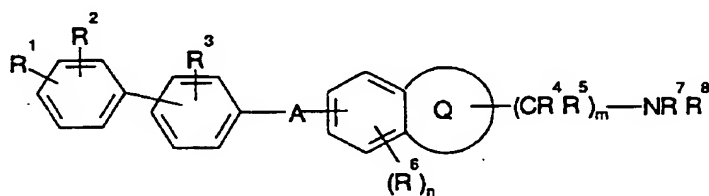
AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

Amide derivatives having 5HT_{1D}-antagonist activity

The present invention relates to novel amide derivatives, processes for their preparation, and pharmaceutical compositions containing them.

- 5 EPA 0 533 266/7/8 disclose a series of benzanilide derivatives which are said to possess 5HT_{1D} receptor antagonist activity. These compounds are said to be of use in the treatment of various CNS disorders.

- A structurally distinct class of compounds have now been discovered and have been found to exhibit 5HT_{1D} antagonist activity. In a first aspect, the present invention
10 therefore provides a compound of formula (I) or a salt thereof:



(I)

15

in which

A is CONR where R is hydrogen or C₁₋₆alkyl;

Q is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;

- 20 R¹ is hydrogen, halogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, COC₁₋₆alkyl, C₁₋₆alkoxy, hydroxy, hydroxyC₁₋₆alkyl, hydroxyC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkoxy, acyl, nitro, trifluoromethyl, cyano, SR⁹, SOR⁹, SO₂R⁹, SO₂NR¹⁰R¹¹, CO₂R¹⁰, CONR¹⁰R¹¹, CO₂NR¹⁰R¹¹, CONR¹⁰(CH₂)_aCO₂R¹¹, (CH₂)_aNR¹⁰R¹¹, (CH₂)_aCONR¹⁰R¹¹, (CH₂)_aNR¹⁰COR¹¹, (CH₂)_aCO₂C₁₋₆alkyl, CO₂(CH₂)_aOR¹⁰, NR¹⁰R¹¹,
25 NR¹⁰CO₂R¹¹, NR¹⁰CONR¹⁰R¹¹, CR¹⁰=NOR¹¹, CNR¹⁰=NOR¹¹, where R¹⁰ and R¹¹ are independently hydrogen or C₁₋₆alkyl and a is 1 to 4 or R¹ is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;

R² and R³ are independently hydrogen, halogen, C₁₋₆alkyl, C₃₋₆cycloalkyl,

- 30 C₃₋₆cycloalkenyl, C₁₋₆alkoxy, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO₂R¹⁰, CONR¹⁰R¹¹, NR¹⁰R¹¹ where R¹⁰ and R¹¹ are as defined for R¹;

R⁴ and R⁵ are independently hydrogen or C₁₋₆alkyl;

R⁶ is halogen, hydroxy, C₁₋₆alkyl or C₁₋₆alkoxy;

R⁷ and R⁸ are independently hydrogen, C₁₋₆alkyl, aralkyl, or together with the nitrogen

- 35 atom to which they are attached form an optionally substituted 5- to 7-membered

heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen or sulphur;

m is 0 to 4; and

n is 0, 1 or 2.

- 5 C₁₋₆alkyl groups, whether alone or as part of another group, may be straight chain or branched.

Suitably R¹ is hydrogen, halogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, COC₁₋₆alkyl, C₁₋₆alkoxy, hydroxy, hydroxyC₁₋₆alkyl, hydroxyC₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkoxy, acyl, nitro, trifluoromethyl, cyano, SR⁹, SOR⁹, SO₂R⁹, SO₂NR¹⁰R¹¹, CO₂R¹⁰,
 10 CONR¹⁰R¹¹, CO₂NR¹⁰R¹¹, CONR¹⁰(CH₂)_aCO₂R¹¹, (CH₂)_aNR¹⁰R¹¹,
 (CH₂)_aCONR¹⁰R¹¹, (CH₂)_aNR¹⁰COR¹¹, (CH₂)_aCO₂C₁₋₆alkyl, CO₂(CH₂)_aOR¹⁰,
 NR¹⁰R¹¹, NR¹⁰CO₂R¹¹, NR¹⁰CONR¹⁰R¹¹, CR¹⁰=NOR¹¹, CNR¹⁰=NOR¹¹, where
 R¹⁰ and R¹¹ are independently hydrogen or C₁₋₆alkyl and a is 1 to 4 or R¹ is an
 15 optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms
 selected from oxygen, nitrogen or sulphur;

When R¹ is a 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms
 selected from oxygen, nitrogen or sulphur suitable heterocyclic rings include thienyl,
 furyl, pyrrolyl, triazolyl, diazolyl, imidazolyl, oxadiazolyl, isothiazolyl, isoxazolyl,
 thiadiazolyl, pyridyl, pyrimidyl and pyrazinyl. The heterocyclic rings can be linked to the
 20 remainder of the molecule via a carbon atom or, when present, a nitrogen atom. Suitable
 substituents for these rings include R² and R³ groups as defined above. Preferably R¹ is
 oxadiazolyl, most preferably a 5-methyl-1,2,4-oxadiazol-3-yl group.

Suitably R² and R³ are independently hydrogen, halogen, C₁₋₆alkyl,
 C₃₋₆cycloalkyl, C₃₋₆cycloalkenyl, C₁₋₆alkoxy, acyl, aryl, acyloxy, hydroxy, nitro,
 25 trifluoromethyl, cyano, CO₂R¹⁰, CONR¹⁰R¹¹, NR¹⁰R¹¹ where R¹⁰ and R¹¹ are as
 defined for R¹. Preferably R² is C₁₋₆alkyl, in particular methyl. Preferably R³ is
 hydrogen.

Suitably A is CONR where R is hydrogen or C₁₋₆alkyl. Preferably A is CONH.

Suitably Q is an optionally substituted 5 to 7-membered heterocyclic ring
 30 containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur. Preferably Q is
 a 5- or 6-membered ring containing one or two heteroatoms. Preferably Q, together with
 the phenyl group to which it is attached, forms an indole, indoline, benzoxazole,
 benzopyran or benzoxazine ring. Suitable optional substituents for the ring Q include
 groups R¹ and R² as defined above. Preferred substituents include C₁₋₆alkyl, particularly
 35 methyl, and carbonyl groups.

Suitably R⁴ and R⁵ are independently hydrogen or C₁₋₆alkyl. Preferably R⁴ and
 R⁵ are both hydrogen.

The group $-(CR^4R^5)_mNR^7R^8$ can be attached to the ring Q at any suitable position, and can be attached to a carbon atom or, when present, a nitrogen atom.

Suitably R^7 and R^8 are independently hydrogen, C_{1-6} alkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen or sulphur. Examples of R^7 and R^8 as heterocyclic rings include pyrrolidine, morpholine, piperazine and piperidine. Optional substituents for such rings include C_{1-6} alkyl. Preferably R^7 and R^8 are both C_{1-6} alkyl, in particular methyl.

Suitably R^6 is halogen, hydroxy, C_{1-6} alkyl or C_{1-6} alkoxy.

Suitably m is 0 to 4, preferably m is 2.

Suitably n is 0, 1 or 2, preferably n is 0.

The groups R^1 , R^2 and R^3 can be attached to their respective rings at any suitable position.

Particularly preferred compounds of the invention include:

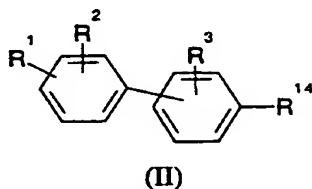
- 15 N-[1-(2-Dimethylaminoethyl)-1H-indol-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
N-[2,3-Dihydro-1-(2-dimethylaminoethyl)-1H-indol-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl) biphenyl-4-carboxamide,
N-[4-(2-Dimethylaminoethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- 20 N-[3-(2-Dimethylaminoethyl)-1H-indol-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
N-[4-(2-Dimethylaminoethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- 25 N-[4-(2-Dimethylaminoethyl)-3,4-dihydro-3-methyl-2H-1,4-benzoxazin-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
N-[4-(2-Dimethylaminoethyl)-3,4-dihydro-2H-benzo[b]pyran-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
N-[3-(2-Dimethylaminoethyl)-2-oxo-2(3H)-benzoxazol-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- 30 N-[5-(2-Dimethylaminoethyl)-2,3,4,5-tetrahydro-1,5-benzoxazepin-7-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
and pharmaceutically acceptable salts thereof.

Preferred salts of the compounds of formula (I) are pharmaceutically acceptable salts. These include acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and the mixtures thereof including racemates. Tautomers of compounds of formula (I) and mixtures thereof also form an aspect of the invention.

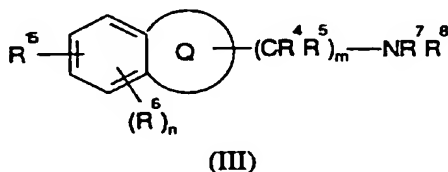
5 In a further aspect the present invention provides a process for the preparation of a compound of formula (I) which comprises.

(a) reaction of a compound of formula (II):



10

with a compound of formula (III):



15

20 in which Q, m, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and n are as defined in formula (I) and R¹⁴ and R¹⁵ contain the appropriate functional group(s) necessary to form the A moiety; and optionally thereafter in any order:

- converting a compound of formula (I) into another compound of formula (I)
- forming a pharmaceutically acceptable salt.

25 Suitably R¹⁴ is an activated carboxylic acid derivative, such as an acyl halide or acid anhydride, and R¹⁵ is an amine group. Activated compounds of formulae (II) or (III) can also be prepared by reaction of the corresponding carboxylic acid with a coupling reagent such as carbonyldiimidazole, dicyclohexylcarbodiimide or diphenylphosphoryl azole. Preferably R¹⁴ is a group COL where L is halo, particularly chloro.

30 A compound of formulae (II) and (III) are typically reacted together in an inert organic solvent such as DMF, THF or dichloromethane at ambient or elevated temperature in the presence of a base such as an alkali metal hydroxide, triethylamine or pyridine.

Intermediate compounds of formulae (II) and (III) are commercially available or

can be prepared using standard procedures such as those outlined in EPA 533266/7/8. Certain intermediate compounds of formulae (II) and (III) are novel and form a further aspect of the invention.

5 It will be appreciated to those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. These groups can be removed by conventional procedures well known in the art.

10 Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection is achieved using standard conditions.

Certain compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures.

15 5HT_{1D} Antagonists, and in particular the compounds of the present invention, are expected to be of use in the treatment of CNS disorders such as mood disorders, including depression, seasonal effective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnesic disorders and age-associated memory impairment; and disorders of eating
20 behaviours, including anorexia nervosa and bulimia nervosa. Other CNS disorders include Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

25 5HT_{1D} Antagonists, and in particular compounds of the present invention, may also be of use in the treatment of endocrine disorders such as hyperprolactinaemia, in the treatment of vasospasm (particularly in the cerebral vasculature) and hypertension, as well as disorders in the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction.

Therefore, the present invention, provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy.

30 The present invention also provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

35 In another aspect the invention provides the use of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of the aforementioned disorders.

In a further aspect the invention provides a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such

treatment of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof.

In particular the invention provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be

accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

5 The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more
10 than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following examples illustrate the preparation of compounds of the invention.

Description 1**1-(2-Dimethylaminoethyl)-6-nitro-1H-indole**

5 A solution of 2-dimethylaminoethyl chloride (0.86g, 8 mmol) in dry toluene (30ml) was added to a mixture of 6-nitroindole (0.63g, 3.9mmol) and potassium t-butoxide (0.44g, 4 mmol) in dry THF (40ml) under an argon atmosphere. The reaction mixture was stirred at room temperature for 19hr, then heated under reflux for 3hr. After cooling the mixture was treated with 10% aqueous Na₂CO₃ solution and extracted with EtOAc. The combined organic layers were dried (Na₂SO₄) and evaporated under reduced pressure to give the
10 title compound (0.89g, 98%).

¹H NMR (250MHz, CDCl₃) δ : 8.31 (s, 1H), 7.97 (dd, 1H), 7.59 (d, 1H), 7.44 (d, 1H) 6.57 (d, 1H), 4.23 (t, 2H), 2.68 (t, 2H), 2.29 (s, 6H).

15 Description 2**6-Amino-1-(2-dimethylaminoethyl)-1H-indole**

A suspension of the product from description 1 (0.14g, 0.6mmol) in EtOH (25ml) was hydrogenated over 10% palladium on charcoal until hydrogen uptake ceased. The catalyst
20 was removed by filtration through kieselguhr and the filtrate concentrated under reduced pressure to give the title compound as a brown oil. (0.14g, 100%).

¹H NMR (200MHz, CDCl₃) δ : 7.3 (d, 1H), 6.81 (s, 1H), 6.52-6.41 (m, 2H), 6.28 (s, 1H), 4.0 (t, 2H), 3.41 (brs, 2H), 2.57 (t, 2H) 2.21 (s, 6H)

25

Description 3**2,3-Dihydro-1-(2-dimethylaminoethyl)-6-nitro-1H-indole**

The product from description 1 (0.5g 2.0mmol) was dissolved in TFA (10ml) and the
30 solution cooled to 0°C and treated with a sodium borohydride pellet (0.12g, 3.0mmol) under an argon atmosphere. After stirring for 19hr at room temperature, the reaction mixture was cooled to 0°C and water was added cautiously until effervescence had ceased. The mixture was evaporated under reduced pressure and the residue neutralised with solid K₂CO₃. The product was extracted into EtOAc. The combined organic layers were dried
35 (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification

by flash column chromatography using CH_2Cl_2 as eluant gave the title compound 0.11g, 22%).

^1H NMR (250MHz, CDCl_3) δ : 7.52 (dd, 1H), 7.18 (d, 1H), 7.09 (d, 1H), 3.58 (t, 2H),
5 3.28 (t, 2H), 3.06 (t, 2H), 2.55 (t, 2H) 2.32 (s, 6H).

Description 4

6-Amino-2,3-dihydro-1-(2-dimethylaminoethyl)-1H-indole

10 Following the procedure outlined in description 2, reaction of the product from description 3 (0.11g, 0.5mmol) afforded the title compound as a brown oil (0.11g, 100%)

^1H NMR (250MHz, CDCl_3) δ : 6.72 (d, 1H), 5.90 (d, 1H), 5.79 (s, 1H), 3.40 (brs, 2H)
15 3.28 (t, 2H), 3.03 (t, 2H), 2.78 (t, 2H), 2.43 (t, 2H), 2.20 (s, 6H)

Description 5

4-(2-Dimethylaminoethyl)-6-nitro-2H-1,4-benzoxazin-3(4H)-one

To a suspension of 6-nitro-2H-1,4-benzoxazin-3(4H)-one (J. Med. Chem. 1989, 32, 1627-
20 1630) 1g, 5.7mmol) in dry THF (20ml) at 0°C under argon, was added NaH (0.16g, 5.7mmol 80% dispersion in mineral oil). A solution of 2-dimethylaminoethyl chloride (2.3 g, 20.8mmol) in dry toluene (15ml) was added and the reaction mixture heated under reflux for 19hr. After cooling, water was added dropwise until effervescence had ceased, then the mixture was separated and the aqueous further extracted with EtOAc. The organic
25 layers were combined, dried (Na_2SO_4) and evaporated under reduced pressure to give a pale brown solid (1.08g, 79%)

^1H NMR (250MHz, CDCl_3) δ : 8.03 (d, 1H), 7.94 (dd, 1H), 7.04 (d, 1H), 4.73 (s, 2H),
30 4.11 (t, 2H) 2.6 (t, 2H), 2.35 (s, 6H).

Description 6

3,4-Dihydro-4-(2-dimethylaminoethyl)-6-nitro-2H-1,4-benzoxazine

Boron trifluoride etherate (2ml, 16.2mmol) was added dropwise to a suspension of sodium
35 borohydride (0.46g, 12mmol) in dry THF (30ml) at 0°C , under argon. After 1 hr, a solution of the product from description 5 (1.08g, 4mmol) in dry THF (20ml) was added. The reaction mixture was heated under reflux for 2hr, then cooled in ice. Aqueous

NaHCO₃ was added dropwise until effervescence ceased, then the solvent was removed under reduced pressure and the residue dissolved in a mixture of EtOH (10ml) and 5N HCl (10ml) and heated under reflux for 45 minutes. After cooling, the solvent was removed under reduced pressure. The residue was treated with saturated K₂CO₃ solution to pH 8, then extracted with EtOAc. The combined extracts were dried (Na₂SO₄) and evaporated under reduced pressure to give the title compound (0.94g, 92%).

¹H NMR (200MHz, CDCl₃) δ : 7.52 (m, 2H), 6.78 (d, 1H), 4.30 (t, 2H), 3.42 (m, 4H), 2.56 (t, 2H), 2.31 (s, 6H)

10

Description 7

6-Amino-3,4-dihydro-4-(2-dimethylaminoethyl)-2H-1,4-benzoxazine

Following the procedure outlined in description 2, reaction of the product from description 6 (0.94g, 4mmol) afforded the title compound as a brown oil (0.84g, 100%).

15

¹H NMR (200MHz, CDCl₃) δ : 6.58 (d, 1H), 6.08 (d, 1H), 5.98 (dd, 1H), 4.13 (t, 2H), 3.35 (m, 6H), 2.50 (t, 2H), 2.30 (s, 6H).

20 Description 8

6-Amino-4-(2-dimethylaminoethyl)-2H-1,4-benzoxazin-3(4H)-one

4-(2-Dimethylaminoethyl)-6-nitro-2H-1,4-benzoxazin-3(4H)-one (D5) (0.175g, 0.6 mmol) was hydrogenated in 1:1 ethanol/acetic acid (20 ml) for 5.5 h. Catalyst was removed by filtration through kieselguhr, and the filtrate was evaporated, dissolved in dichloromethane, washed with K₂CO₃ solution, dried (Na₂SO₄) and evaporated again to give the title compound (0.145g, 93%) as a yellow-brown solid.

25

¹H NMR (200 MHz, CDCl₃) δ (ppm): 6.79 (d, 1H), 6.39 (d, 1H), 6.32 (dd, 1H), 4.50 (s, 2H), 3.99 (t, 2H), 3.61 (bs, 2H), 2.53 (t, 2H), 2.32 (s, 6H)

30

Description 9

3-Methyl-6-nitro-2H-1,4-benzoxazine

To a stirred solution of 2-amino-4-nitrophenol (1.0g, 6.48 mmol) in acetone (250 ml) was added K₂CO₃ (1.35g, 9.73 mmol). The reaction mixture was stirred at room temperature under Ar for 3 h. Chloroacetone (0.52 ml, 6.48 mmol) and K₂CO₃ (1.35g, 9.73 mmol)

35

were then added and the mixture was heated to reflux under Ar for 3 h, then allowed to cool and filtered through kieselguhr. The filtrate was concentrated *in vacuo* to afford the title compound as a dark red solid (1.25g, 100%)

- 5 ^1H NMR (200 MHz, CDCl_3) δ (ppm): 8.15 (d, 1H), 8.02 (dd, 1H), 6.90 (d, 1H), 4.70 (s, 2H), 2.20 (s, 3H).

Description 10

3,4-Dihydro-3-methyl-6-nitro-2H-1,4-benzoxazine

10

3-Methyl-6-nitro-2H-1,4-benzoxazine (D9, 1.25g, 6.47 mmol) in ethanol (30 ml) was treated portionwise over 10 minutes with sodium tetrahydroborate (0.88g, 23.2 mmol). The reaction mixture was stirred at room temperature for 2 hours, then treated with water (60 ml) and dilute HCl (2 ml) and concentrated *in vacuo*. The residue was basified using
15 saturated aqueous K_2CO_3 solution (60 ml) and extracted using ethyl acetate (3 x 100 ml). Combined organic extracts were dried (Na_2SO_4) and then concentrated *in vacuo* to afford the title compound as a deep red crystalline solid (1.00g, 80%).

- 20 ^1H NMR (200 MHz, CDCl_3) δ (ppm): 7.58 (dd, 1H), 7.48 (d, 1H), 6.80 (d, 1H), 4.30 (m, 1H), 4.05 (b, 1H), 3.85 (dd, 1H), 3.55 (m, 1H), 1.25 (d, 3H).

Description 11

4-(2-Chloroacetyl)-3,4-dihydro-3-methyl-6-nitro-2H-1,4-benzoxazine

- 25 A stirred solution of 3,4-dihydro-3-methyl-6-nitro-2H-1,4-benzoxazine (D10, 347 mg, 1.78 mmol) and triethylamine (0.50 ml, 3.55 mmol) in chloroform (10 ml) at 0°C under Ar was treated with chloroacetyl chloride (0.28 ml, 3.55 mmol). The reaction mixture was stirred at room temperature for 2 hours, then treated with water (100 ml) and acidified using 5M HCl. The organic phase was extracted using chloroform (2 x 100 ml).
30 Combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a brown oil (461 mg, 95%).

^1H NMR (200 MHz, CDCl_3) δ (ppm): 8.28 (b, 1H), 8.03 (dd, 1H), 7.05 (d, 1H), 4.75 (b, 1H), 4.30 (m, 4H), 1.30 (d, 3H).

35

Description 12**3,4-Dihydro-4-(2-dimethylaminoacetyl)-3-methyl-6-nitro-2H-1,4-benzoxazine**

- 4-(2-Chloroacetyl)-3,4-dihydro-3-methyl-6-nitro-2H-1,4-benzoxazine (D11, 461 mg, 1.70 mmol) in ethanol (20 ml) was treated with dimethylamine (4ml of 5.6 M solution in ethanol). The suspension was left to stir at room temperature for 48 hours. The resulting mixture was concentrated *in vacuo* to afford the title compound as a brown solid (422 mg, 88%).
- ¹H NMR (200 MHz, CDCl₃) δ (ppm): 9.02 (s, 1H), 8.00 (dd, 1H), 7.00 (d, 1H), 5.00 (b, 1H), 4.29 (ABX, 2H), 3.45 (d, 1H), 3.19 (m, 1H), 2.38 (s, 6H), 1.29 (d, 3H).

Description 13**6-Amino-3,4-dihydro-4-(2-dimethylaminoacetyl)-3-methyl-2H-1,4-benzoxazine**

- 3,4-Dihydro-4-(2-dimethylaminoacetyl)-3-methyl-6-nitro-2H-1,4-benzoxazine (D12, 422 mg, 1.51 mmol) was hydrogenated in ethanol (30 ml) over 10% palladium-charcoal (200 mg) at room temperature and atmospheric pressure for 18 hours. The catalyst was removed by filtration through kieselguhr, and the filtrate concentrated *in vacuo* to afford the title compound as a brown solid (304 mg, 80%). This was used without purification in the next step.

Description 14**6-Amino-3,4-dihydro-4-(2-dimethylaminoethyl)-3-methyl-2H-1,4-benzoxazine**

- To a stirred suspension of lithium aluminium hydride (70 mg, 1.83 mmol) in dry tetrahydrofuran (THF) (60 ml) at 0°C under Ar was added dropwise, a solution of 6-amino-3,4-dihydro-4-(2-dimethylaminoacetyl)-3-methyl-2H-1,4-benzoxazine (D13, 304 mg, 1.22 mmol) in THF (10 ml). The reaction mixture was heated under reflux for 2.5 hours, then allowed to cool to room temperature, after which it was treated with water (0.07 ml), 10% NaOH solution (0.07 ml) and water (0.21 ml). The mixture was filtered through kieselguhr and the filtrate dried (Na₂SO₄) and concentrated *in vacuo* to afford a yellow oil (160 mg). This was chromatographed on silica gel eluting with 5-40% MeOH/CH₂Cl₂ to afford the title compound as a dark brown oil (61.7 mg, 22%).
- ¹H NMR (200 MHz, CDCl₃) δ (ppm): 6.60 (d, 1H), 6.03 (d, 1H), 5.95 (dd, 1H), 3.95 (m, 2H), 3.51-3.12 (m, 5H), 2.50 (t, 2H), 2.30 (s, 6H), 1.20 (d, 3H)

Description 15**Methyl (3,4-dihydro-2H-benzo[b]pyran-4-ylidene)acetate, E- and Z- isomers**

5 Sodium hydride (80% in mineral oil, 4.90g, 0.16 mol) was stirred under Ar in dry THF (200 ml) as trimethyl phosphonoacetate (26.2 ml, 0.16 mol) was added in dry THF (50 ml) maintaining the temperature at ca. 20° C by standing in ice. 4-Chromanone (10.92g, 0.07 mol) was added in dry THF (100 ml), and the mixture was then stirred at ambient
10 dichloromethane. The extract was dried (Na₂SO₄) and evaporated to an orange oil, which was chromatographed on silica gel, eluting with 10% ethyl acetate in petroleum ether (b.p. 60-80° C). This gave pure E-isomer (4.55g), pure Z-isomer (2.90g), and a mixture of the two isomers (1.66g) (total yield: 9.11g, 60%).

15 **E-isomer:** ¹H NMR (200 MHz, CDCl₃) δ (ppm): 7.61 (dd, 1H), 7.30 (m, 1H), 6.90 (m, 2H), 6.35 (s, 1H), 4.24 (t, 2H), 3.76 (s, 3H), 3.40 (td, 2H).

Z-isomer: ¹H NMR (200 MHz, CDCl₃) δ (ppm): 7.79 (dd, 1H), 7.26 (td, 1H), 6.85 (m, 2H), 5.70 (s, 1H), 4.38 (t, 2H), 3.75 (s, 3H), 2.65 (td, 2H).

20

Description 16**Methyl (3,4-dihydro-2H-benzo[b]pyran-4-yl)acetate**

A mixture of E- and Z-methyl (3,4-dihydro-2H-benzo[b]pyran-4-ylidene)acetate (D15)
25 (5.14g, 25 mmol) was hydrogenated over 10% palladium on charcoal (1.00g) in ethanol (100ml) for 2 h. Catalyst was filtered off onto kieselguhr, and the filtrate was evaporated to give the title compound (4.64g, 89%) as a colourless oil.

¹H NMR (200 MHz, CDCl₃) δ (ppm): 7.1 (m, 2H), 6.85 (m, 2H), 4.2 (m, 2H), 3.73 (s, 3H), 3.36 (sextet, 1H), 2.82 and 2.55 (ABX, 2H), 2.17 (m, 1H), 1.86 (m, 1H)
30

Description 17**(3,4-Dihydro-2H-benzo[b]pyran-4-yl)acetic acid**

5 Methyl (3,4-dihydro-2H-benzo[b]pyran-4-yl)acetate (D16) (4.64g, 22 mmol) was stirred in ethanol (50 ml) as sodium hydroxide (1.80g, 45 mmol) was added in water (10 ml). The mixture was stirred for 1 h, concentrated *in vacuo*, diluted with water, and acidified with 5M HCl. The white solid, the title compound (3.69g, 85%), was filtered off and dried.

10 ¹H NMR (200 MHz, CDCl₃) δ (ppm): 7.13 (m, 2H), 6.86 (m, 2H), 4.21 (m, 2H), 3.38 (sextet, 1H), 2.89 and 2.60 (ABX, 2H), 2.20 (m, 1H), 1.92 (m, 1H).

Description 18**N,N-Dimethyl-(3,4-dihydro-2H-benzo[b]pyran-4-yl)acetamide**

15 (3,4-Dihydro-2H-benzo[b]pyran-4-yl)acetic acid (D17) (1.89g, 9.8 mmol) was stirred at reflux under Ar in thionyl chloride (20 ml) for 45 min, cooled and evaporated to give a brown oil. This was dissolved in dichloromethane (30 ml), and dimethylamine (40% aqueous solution, 5 ml) was added. This mixture was stirred for 30 min, treated with dilute Na₂CO₃ solution (50 ml), and separated. The organic portion was dried (Na₂SO₄) and evaporated to give the title compound (2.22g, 100%) as a brown oil.

25 ¹H NMR (250 MHz, CDCl₃) δ (ppm): 7.11 (m, 2H), 6.85 (m, 2H), 4.19 (m, 2H), 3.48 (sextet, 1H), 3.00 (s, 3H), 2.96 (s, 3H), 2.77 and 2.56 (ABX, 2H), 2.22 (m, 1H), 1.87 (m, 1H).

Description 19**N,N-Dimethyl-(6-amino-3,4-dihydro-2H-benzo[b]pyran-4-yl) acetamide and N,N-dimethyl-(8-amino-3,4-dihydro-2H-benzo[b]pyran-4-yl)acetamide**

30 N,N-Dimethyl-(3,4-dihydro-2H-benzo[b]pyran-4-yl)acetamide (D18) (0.84g, 3.8 mmol) was stirred in acetic anhydride (10 ml) as copper (II) nitrate trihydrate (1.23g, 5.1 mmol) was added, cooling the mixture by standing in a cold water bath. The mixture was stirred for 1h, poured into K₂CO₃ solution, and extracted with dichloromethane. The extract was dried (Na₂SO₄) and evaporated, giving a mixture of the intermediate nitro compounds (1.04g). This was hydrogenated over 10% palladium on charcoal (0.50g) in ethanol (25 ml)/acetic acid (10 ml) for 6 h. Catalyst was filtered off onto kieselguhr, and the filtrate

was concentrated, diluted with dichloromethane, washed with NaHCO₃ solution, dried (Na₂SO₄) and evaporated to give a dark oil (0.50g). Chromatography on silica gel, eluting with 0-4% methanol in dichloromethane gave the 8-amino compound (0.177g, 19%), followed by the 6-amino compound (0.091g, 10%), both as light brown gums.

5

8-Amino isomer: ¹H NMR (200 MHz, CDCl₃) δ(ppm): 6.71 (d, 1H), 6.55 (m, 2H), 4.24 (m, 2H), 3.7 (b, 2H), 3.43 (sextet, 1H), 2.98 (s, 3H), 2.96 (s, 3H), 2.77 and 2.53 (ABX, 2H), 2.21 (m, 1H), 1.85 (m, 1H).

10 **6-Amino isomer:** ¹H NMR (200 MHz, CDCl₃) δ(ppm): 7.63 (d, 1H), 6.50 (m, 2H), 4.11 (m, 2H), 3.5 (b, 2H), 3.39 (sextet, 1H), 2.99 (s, 3H), 2.96 (s, 3H), 2.72 ad 2.53 (ABX, 2H), 2.17 (m, 1H), 1.78 (m, 1H).

Description 20

15 **2-(6-Amino-3,4-dihydro-2H-benzo[b]pyran-4-yl)-N,N-dimethylethylamine**

N,N-Dimethyl-(6-amino-3,4-dihydro-2H-benzo[b]pyran-4-yl)acetamide (D19) (0.019g, 0.39 mmol) was added in dry THF (8 ml) to a suspension of lithium aluminium hydride (0.030g, 0.79 mmol) in dry THF (2 ml). The mixture was stirred at reflux under Ar for 20 3h, cooled and treated successively with water (0.03 ml), 10% NaOH (0.03 ml) and water (0.09 ml). It was then diluted with ethyl acetate, dried (Na₂SO₄) and filtered. Evaporation then gave the title compound (0.068g, 79%) as a brown gum.

¹H NMR (200 MHz, CDCl₃) δ(ppm): 6.62 (d, 1H), 6.50 (m, 2H), 4.10 (m, 2H), 3.35 (b, 25 2H), 2.80 (sextet, 1H), 2.36 (m, 2H), 2.25 (s, 6H), 2.02 (m, 2H), 1.72 (m, 2H)

Description 21

5-Nitro-2(3H)-benzoxazolone

30 A stirred solution of 2-amino-4-nitrophenol (1.50g, 9.7 mmol) and 1,1'-carbonyldiimidazole (1.74g, 10.7 mmol) in N,N-dimethylformamide (20 ml) was heated at 80° C under Ar for 2 hours. The cooled reaction mixture was then poured into water (300 ml) and the resulting solid was filtered off and dried, affording the title compound as a beige powder (1.22g, 69%).

35

¹H NMR (200 MHz, d⁶DMSO) δ (ppm): 8.06 (dd, 1H), 7.85 (d, 1H), 7.53 (d, 1H), 3.50 (b, 1H)

Description 22**3-(2-Dimethylaminoethyl)-5-nitro-2(3H)-benzoxazolone**

- 5 To a stirred solution of 2-dimethylaminoethyl chloride hydrochloride (4.88g, 34 mmol) in water (50 ml) was added solid anhydrous K_2CO_3 until completely saturated. This suspension was then extracted with toluene (2 x 50 ml). The combined extract was dried (Na_2SO_4) and the resulting solution added dropwise to a stirred suspension of 5-nitro-2(3H)-benzoxazolone (D21) (1.22g, 6.8 mmol) and sodium hydride (0.22g, 7.45 mmol) in
- 10 tetrahydrofuran (100 ml) at 0° C under Ar. The reaction mixture was heated under reflux for 3 hours. Cold water was run into the cooled mixture until effervescence had ceased, then the mixture was acidified using 5M HCl and washed with ethyl acetate (2 x 100 ml). The aqueous solution was basified using saturated K_2CO_3 solution and then extracted using ethyl acetate (2 x 100 ml). The combined organic extracts were dried (Na_2SO_4) and
- 15 concentrated *in vacuo* to afford the title compound as a yellow solid (0.47g, 27%).

1H NMR (200 MHz, $CDCl_3/d^6DMSO$) δ (ppm): 8.12 (dd, 1H), 7.98 (d, 1H), 7.38 (d, 1H), 4.00 (t, 2H), 2.70 (t, 2H), 2.30 (s, 6H)

20 **Description 23**

5-Amino-3-(2-dimethylaminoethyl)-2(3H)-benzoxazolone

- A solution of 3-(2-dimethylaminoethyl)-5-nitro-2(3H)-benzoxazolone (D22) (0.47g, 1.87 mmol) in ethanol (60 ml) was hydrogenated over 10% palladium-charcoal (0.2 g) at
- 25 atmospheric pressure and temperature for 18 hours. The catalyst was removed by filtration through kieselguhr and the filtrate concentrated *in vacuo* to afford the title compound as a green oil (0.36g, 88%).

- 1H NMR (200 MHz, $CDCl_3$) δ (ppm): 6.95 (d, 1H), 6.41 (d, 1H), 6.35 (s, 1H), 3.85 (t, 2H), 3.70 (b, 2H), 2.62 (t, 2H), 2.31 (s, 6H)
- 30

Description 24**7-Nitro-2,3,4,5-tetrahydro-1,5-benzoxazepine**

2,3,4,5-Tetrahydro-1,5-benzoxazepine (Zh. Obshch. Khim. 1963, 33, 322) (340 mg, 2.27 mmol) was treated with 5M sulphuric acid (0.5 ml) and ethanol (10 ml). This solution was stirred for five minutes and then concentrated *in vacuo* to afford a brown oil, which was dissolved in concentrated sulphuric acid (10 ml) and cooled to 10° C under Ar. This solution was treated with potassium nitrate (0.29g, 2.84 mmol) over 20 minutes maintaining the temperature between 15-18° C. The reaction mixture was then stirred at room temperature for 1.5 hours, after which it was added to an ice/water mixture (~100 ml). This solution was basified using 40% sodium hydroxide solution, and then extracted using ethyl acetate. The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to afford a yellow/brown solid. This was chromatographed on silica gel eluting with ethyl acetate to afford the title compound as an orange solid (174.6 mg, 39%).

¹H NMR (200 MHz, CDCl₃) δ (ppm): 7.61 (m, 2H), 6.95 (d, 1H), 4.25 (t, 2H), 3.96 (b, 1H), 3.35 (m, 2H), 2.10 (m, 2H)

Description 25**7-Amino-5-(2-dimethylaminoethyl)-2,3,4,5-tetrahydro-1,5-benzoxazepine**

The title compound was prepared from 7-nitro-2,3,4,5-tetrahydro-1,5-benzoxazepine (D24) as a brown oil (132 mg, 82%) using the methodology of Descriptions 11,12,13 and 14.

¹H NMR (200 MHz, CDCl₃) δ (ppm): 6.75 (m, 1H), 6.13 (m, 2H), 4.00 (m, 2H), 3.20 (m, 6H), 2.55 (t, 2H), 2.30 (s, 6H), 1.95 (t, 2H)

Example 1**N-[1-(2-Dimethylaminoethyl)-1H-indol-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide**

2'-Methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxylic acid (E.P.0533268-A1) (0.19g, 0.7mmol) was suspended in CH₂Cl₂ (15ml) and treated with oxalylchloride (0.065ml, 0.074mmol) followed by a drop of DMF. The mixture was stirred at room temperature for 1hr, then evaporated under reduced pressure to give a pale yellow solid.

The solid was redissolved in dichloromethane (10ml) and added to a solution of the product from description 2 (0.14g, 0.7mmol) in CH₂Cl₂ (10ml) containing Et₃N (0.19ml, 1.4mmol) under argon. After 19hr at room temperature, the reaction mixture was treated with water (20ml), extracted with CH₂Cl₂ and the combined organic layers were dried (Na₂SO₄) and evaporated under reduced pressure to give a brown oil which was purified by flash column chromatography using CH₂Cl₂ as eluant. The title compound was isolated as a white solid. (90mg, 30%)

¹H NMR (250MHz, CDCl₃) δ : 8.40 (s, 1H) 8.20 (s, 1H) 7.99-7.90 (m, 4H), 7.53 (d, 1H), 7.39 (d, 2H), 7.30 (d, 1H), 7.12 (d, 1H), 7.08 (dd, 1H), 6.46 (d, 1H), 4.18 (t, 2H), 2.71-2.65 (m, 5H), 2.31 (s, 3H), 2.25 (s, 6H).

Example 2

N-[2,3-Dihydro-1-(2-dimethylaminoethyl)-1H-indol-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl) biphenyl-4-carboxamide

Following the procedure outlined in Example 1, reaction of the product from description 4 (0.11g, 0.5mmol) afforded the title compound as a white solid (90mg, 48%)

¹H NMR (250MHz, CDCl₃) δ: 8.01 (s, 1H), 7.99-7.92 (m, 3H), 7.80 (s, 1H), 7.48 (d, 2H), 7.38 (d, 1H), 7.03 (m, 2H), 6.79 (dd, 1H), 3.48 (t, 2H), 3.30 (t, 2H), 2.98 (t, 2H), 2.69 (s, 3H), 2.64 (t, 2H), 2.38 (s, 6H) 2.35 (s, 3H).

Example 3

N-[4-(2-Dimethylaminoethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

Following the procedure outlined in Example 1 reaction of the product from description 7 (0.16g, 0.7mmol) afforded the title compound as a pale yellow solid (0.11g, 39%).

¹H NMR (250MHz, CDCl₃) δ : 8.02 (s, 1H), 7.98 (m, 3H), 7.78 (s, 1H), 7.48 (d, 2H), 7.35 (d, 1H), 7.22 (s, 1H), 6.77 (s, 2H), 4.23 (t, 2H), 3.45 (m, 4H), 2.70 (s, 3H), 2.59 (t, 2H), 2.35 (s, 3H), 2.31 (s, 6H)

Example 4

N-[3-(2-Dimethylaminoethyl)-1H-indol-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

- 5 The title compound was prepared from 5-amino-3-(2-dimethylaminoethyl)-1H-indole (J.E. Macor, Syn Comm. 1993, 23, 65) using the procedure of Example 1.

¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.65 (s, 1H), 8.25 (s, 1H), 8.00-7.85 (m, 6H), 7.45 (d, 2H), 7.35-7.30 (m, 2H), 6.95 (s, 1H), 2.90 (t, 2H), 2.70-2.50 (m, 8H), 2.30 (s, 6H).

Example 5

N-[4-(2-Dimethylaminoethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

- 15 2'-Methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxylic acid (EP 0553268A1) (0.188g, 0.64 mmol) was converted to the acyl chloride by stirring at reflux under Ar in thionyl chloride (10 ml) for 45 min, cooling, and then evaporating to dryness. This was reacted with 6-amino-4-(2-dimethylaminoethyl)-1,4-benzoxazin-3(4H)-one (D8) (0.150g, 0.64 mmol) following the procedure of Example 1. This gave the title compound (0.247g, 75%) as a white foam, which was converted to the oxalate, a white solid.

¹H NMR (oxalate, 250 MHz, d₆-DMSO) δ(ppm): 10.40 (s, 1H), 8.09 (d, 2H), 8.00 (s, 1H), 7.94 (d, 1H), 7.72 (d, 1H), 7.58 (d, 2H), 7.52 (dd, 1H), 7.46 (d, 1H), 7.05 (d, 1H), 4.68 (s, 2H), 4.23 (t, 2H), 3.23 (t, 2H), 2.80 (s, 6H), 2.69 (s, 3H), 2.28 (s, 3H)

m.s. (m/z) M⁺ 511. C₂₉H₂₉N₅O₄ requires M⁺ 511

Example 6

- 30 **N-[4-(2-Dimethylaminoethyl)-3,4-dihydro-3-methyl-2H-1,4-benzoxazin-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide**

2'-Methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxylic acid (EP 0533268A1) (77 mg, 0.26 mmol) was treated with thionyl chloride (5 ml) and the mixture heated under reflux under Ar for 1 hour, then concentrated *in vacuo* to afford a yellow solid. This was dissolved in dichloromethane (5 ml) and treated with a solution of 6-amino-3,4-dihydro-4-(2-dimethylaminoethyl)-3-methyl-2H-1,4-benzoxazine (D14, 61.7 mg, 0.26 mmol) and

triethylamine (0.11 ml, 0.78 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at room temperature under Ar for 24 hours, then washed with brine/saturated potassium carbonate solution (30 ml of a 1:1 solution). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown oil. This was
5 chromatographed on SiO_2 , eluting with 0-8% methanol/dichloromethane to afford the title compound as a light yellow oil (72.2 mg, 54%).

^1H NMR (200 MHz, CDCl_3) δ (ppm): 7.95 (m, 4H), 7.81 (s, 1H), 7.45 (d, 2H), 7.34 (d, 1H), 7.18 (s, 1H), 6.78 (m, 2H), 4.01 (m, 2H), 3.60-3.25 (m, 3H), 2.70 (s, 3H), 2.58 (t, 2H), 2.35 (s, 9H), 1.25 (d, 3H).
10

Example 7

N-[4-(2-Dimethylaminoethyl)-3,4-dihydro-2H-benzo[b]pyran-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide
15

The title compound was prepared from 2-(6-amino-3,4-dihydro-2H-benzo[b]pyran-4-yl)-N,N-dimethylethylamine (D20) (0.068 g, 0.31 mmol), following the procedure of Example 1, as a yellow-brown gum, in 36% yield. This was converted to the oxalate, a buff solid.
20

^1H NMR (oxalate, 200 MHz, d_6 -DMSO) δ (ppm): 10.24 (s, 1H), 8.1-7.9 (m, 4H), 7.72 (m, 1H), 7.58 (d, 2H), 7.47 (d, 2H), 6.77 (d, 1H), 4.15 (m, 2H), 3.14 (t, 2H), 2.91 (m, 1H), 2.76 (s, 6H), 2.70 (s, 3H), 2.37 (s, 3H), 2.2-1.75 (m, 4H)

25 M.S. (m.z) M^+ 496. $\text{C}_{30}\text{H}_{32}\text{N}_4\text{O}_3$ requires M^+ 496

Example 8

N-[3-(2-Dimethylaminoethyl)-2-oxo-2(3H)-benzoxazol-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide
30

2'-Methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxylic acid (EP 0553268 A1) (245 mg, 0.83 mmol) was stirred in thionyl chloride (5 ml) at gentle reflux under Ar for 1 hour and then concentrated *in vacuo* to dryness. The solid was dissolved in dichloromethane (5 ml) and added to a stirred solution of 5-amino-3-(2-dimethylaminoethyl)-2(3H)-benzoxazolone (D23) (183.5 mg, 0.83 mmol) in
35 dichloromethane (5 ml) containing triethylamine (0.24 ml, 2.5 mmol). The reaction mixture was stirred at room temperature under Ar for 48 hours, then washed with

saturated potassium carbonate solution/brine (100 ml of 1:1 solution).

The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* affording an off-white solid. This was chromatographed on silica gel eluting with 5% methanol/dichloromethane affording the title compound as a white solid (225 mg, 55%).

5

^1H NMR (200 MHz, CDCl_3) δ (ppm): 8.15 (s, 1H), 7.95 (m, 6H), 7.50 (d, 1H), 7.41 (d, 1H), 7.15 (d, 1H), 7.00 (dd, 1H), 3.95 (t, 2H), 2.70 (s+t, 5H), 2.35 (s, 3H), 2.29 (s, 6H)

Example 9

10

N-[5-(2-Dimethylaminoethyl)-2,3,4,5-tetrahydro-1,5-benzoxazepin-7-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide

15

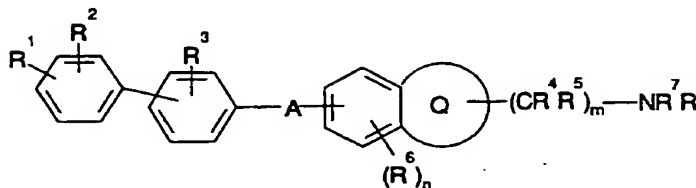
The title compound was prepared from 7-amino-5-(2-dimethylaminoethyl)-2,3,4,5-tetrahydro-1,5-benzoxazepine (D25) as a brown oil (56 mg, 20%) using the method of Example 6.

20

^1H NMR (200 MHz, CDCl_3) δ (ppm): 8.10 (s, 1H), 7.96 (m, 5H), 7.44 (d, 1H), 7.30 (m, 3H), 6.90 (d, 1H), 4.12 (t, 2H), 3.40 (m, 4H), 2.70 (t, 5H), 2.40 (s, 6H), 2.32 (s, 3H), 2.02 (t, 2H)

CLAIMS:

1. A compound of formula (I) or a salt thereof:



(I)

10 in which

A is $CONR$ where R is hydrogen or C_{1-6} alkyl;

Q is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;

15 R^1 is hydrogen, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, COC_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, hydroxy C_{1-6} alkyl, hydroxy C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, acyl, nitro, trifluoromethyl, cyano, SR^9 , SOR^9 , SO_2R^9 , $SO_2NR^{10}R^{11}$, CO_2R^{10} , $CONR^{10}R^{11}$, $CO_2NR^{10}R^{11}$, $CONR^{10}(CH_2)_aCO_2R^{11}$, $(CH_2)_aNR^{10}R^{11}$, $(CH_2)_aCONR^{10}R^{11}$, $(CH_2)_aNR^{10}COR^{11}$, $(CH_2)_aCO_2C_{1-6}$ alkyl, $CO_2(CH_2)_aOR^{10}$, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CONR^{10}R^{11}$, $CR^{10}=NOR^{11}$, $CNR^{10}=NOR^{11}$, where R^{10} and R^{11}

20 are independently hydrogen or C_{1-6} alkyl and a is 1 to 4 or R^1 is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;

R^2 and R^3 are independently hydrogen, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl,

25 C_{3-6} cycloalkenyl, C_{1-6} alkoxy, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^{10} , $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are as defined for R^1 ;

R^4 and R^5 are independently hydrogen or C_{1-6} alkyl;

R^6 is halogen, hydroxy, C_{1-6} alkyl or C_{1-6} alkoxy;

R^7 and R^8 are independently hydrogen, C_{1-6} alkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered

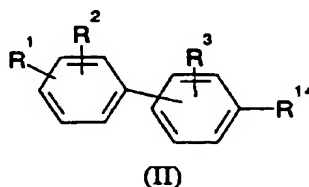
30 heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen or sulphur;

m is 0 to 4; and

n is 0, 1 or 2.

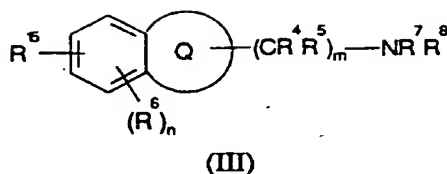
2. A compound according to claim 1 in which R^1 is oxadiazole.

3. A compound according to claim 1 or 2 in which R^2 is C_{1-6} alkyl.
4. A compound according to any one of claims 1 to 3 in which R^3 is hydrogen
5. A compound according to any one of claims 1 to 4 in which R^4 and R^5 are both hydrogen and m is 2.
- 5 6. A compound according to any one of claims 1 to 5 in which n is 0.
7. A compound according to claim 1 which is:
- N-[1-(2-Dimethylaminoethyl)-1H-indol-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- N-[2,3-Dihydro-1-(2-dimethylaminoethyl)-1H-indol-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- 10 N-[4-(2-Dimethylaminoethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- N-[3-(2-Dimethylaminoethyl)-1H-indol-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- 15 N-[4-(2-Dimethylaminoethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- N-[4-(2-Dimethylaminoethyl)-3,4-dihydro-3-methyl-2H-1,4-benzoxazin-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- N-[4-(2-Dimethylaminoethyl)-3,4-dihydro-2H-benzo[b]pyran-6-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- 20 N-[3-(2-Dimethylaminoethyl)-2-oxo-2(3H)-benzoxazol-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- N-[5-(2-Dimethylaminoethyl)-2,3,4,5-tetrahydro-1,5-benzoxazepin-7-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
- 25 and pharmaceutically acceptable salts thereof.
8. A process for the preparation of a compound of formula (I) which comprises
- (a) reaction of a compound of formula (II):



30

with a compound of formula (III):



- 5 in which Q, m, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and n are as defined in formula (I) and R¹⁴ and R¹⁵ contain the appropriate functional group(s) necessary to form the A moiety; and optionally thereafter in any order:
- converting a compound of formula (I) into another compound of formula (I)
 - forming a pharmaceutically acceptable salt.
- 10 9. A compound according to any one of claims 1 to 7 for use in therapy.
10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 in association with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 95/01890

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/12 A61K31/55 A61K31/535 A61K31/40 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP-A-0 533 266 (GLAXO GROUP LTD) 24 March 1993 see the whole document ---	1-10
A	EP-A-0 533 267 (GLAXO GROUP LTD) 24 March 1993 see the whole document ---	1-10
A	EP-A-0 533 268 (GLAXO GROUP LTD) 24 March 1993 see the whole document ---	1-10
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

6 September 1995

Date of mailing of the international search report

- 3. 10. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Steendijk, M

INTERNATIONAL SEARCH REPORT

Intern: 11 Application No
PCT/EP 95/01890

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	NEUROPHARMACOLOGY (NEPHBW,00283908);95; VOL.34 (4); PP.383-92, MERCK SHARP DOHME RESEARCH LABORATORIES;NEUROSCIENCE RESEARCH CENTRE;. ESSEXW; CM20 2QR; UK (GB). HUTSON P H ET AL 'The effects of GR127935, a putative 5-HT1D receptor antagonist, on brain 5-HT metabolism, extracellular 5-HT concentration and behavior in the guinea pig' see the whole document ---	1-10
P,A	NEUROPHARMACOLOGY (NEPHBW,00283908);95; VOL.34 (4); PP.377-82, GLAXO RESEARCH DEVELOPMENT LTD.;EXTERNAL SCIENTIFIC AFFAIRS; STEVENAGE; SG1 2NY; UK (GB). SKINGLE M ET AL 'Effects of the 5-HT1D receptor antagonist GR127935 on extracellular levels of 5-HT in the guinea pig frontal cortex as measured by microdialysis' see the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern: al Application No

PCT/EP 95/01890

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0533266	24-03-93	AU-A- 2452992	25-03-93
		CA-A- 2078506	19-03-93
		HU-A- 66319	28-11-94
		JP-A- 6107649	19-04-94
		US-A- 5356893	18-10-94
		ZA-A- 9207107	08-09-93
EP-A-0533267	24-03-93	AU-A- 2452892	25-03-93
		AU-A- 2568792	27-04-93
		CA-A- 2078507	19-03-93
		CN-A- 1073430	23-06-93
		CZ-A- 9400611	16-11-94
		WO-A- 9306084	01-04-93
		FI-A- 941261	17-03-94
		JP-A- 6107637	19-04-94
		NO-A- 940974	17-03-94
		US-A- 5358948	25-10-94
EP-A-0533268	24-03-93	AP-A- 303	28-01-94
		AU-B- 656021	19-01-95
		AU-A- 2453092	25-03-93
		CA-A- 2078505	19-03-93
		HU-A- 65608	28-07-94
		JP-A- 6116251	26-04-94
		NZ-A- 244373	28-03-95
		US-A- 5340810	23-08-94
		ZA-A- 9207108	08-09-93
		CN-A- 1076195	15-09-93

This Page Blank (uspto)

This Page Blank (uspto)